

**REMARKS**

Applicants respectfully request entry of the current amendments to the claims. Applicants believe that the present amendments place all of the claims in condition for allowance, or in a better condition for appeal.

In the June 16, 2003 Office Action, the Examiner indicated that claims 1-8 are now under examination, having withdrawn the requirement for restriction previously mailed (and responded to) in this case. By virtue of this response, Claims 1, 2, 4 and 7 have been amended, Claim 8 has been canceled, and Claims 9-11 are newly presented.

**Amendments**

Claims 1 and 4 have been amended to remove the term “derivative thereof” and to make singular the reference to certain salts, hydrates, solvates and N-oxides of the claimed compounds.

Similarly, Claim 2 has been amended to make singular the phrase relating to enantiomers, diastereomers and pharmaceutically acceptable salts. Claim 2 has also been amended to revert the right-most Ar<sup>1</sup> group to Ar<sup>2</sup>, as originally filed. Support for this reversion can be found at page 6, formula II, between paragraphs [0014] and [0015] and in paragraph [0017].

Claim 7 has been amended to depend on Claim 5, rather than on Claim 6, as originally presented. The need for such amendment is readily apparent from the subject matter of the claims.

Claim 8 has been canceled solely in the interest of advancing prosecution of the claims.

New Claims 9 and 10 are added to bring out the feature of the invention that pharmaceutical compositions of the invention are useful in the treatment of a number of conditions involving inflammation in which the extravasation of leukocytes plays a role. Support for this feature of the invention can be found, for example at paragraphs [00141] and [00142] at page 51 of the instant specification.

New Claims 11 and 12 are added to bring out the feature of the invention that particularly useful compounds have the characteristics indicated. Support for these particularly selected compounds can be found, for example, at p. 22, paragraphs [0061] and [0064] thereof, p. 23,

paragraphs [0066], [0067], [0069], and [0070] thereof, and p. 48, paragraph [00136] thereof.

The foregoing amendments and/or cancellation of certain claims is not to be construed as a dedication to the public of any of the subject matter of the claims as previously presented. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in a future continuation and/or divisional application. No new matter has been added.

**Rejections under 35 U.S.C. § 112, second paragraph**

Claims 1-8 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner's objections and the applicants' response and/or amendment to address such objections are detailed below:

Specifically, the Examiner objected to applicants' recitation of "derivative thereof" in Claim 1, as indefinite. Applicants have amended Claims 1 and 4 to remove this phrase.

In addition, the Examiner objected to Claims 1, 2 and 4, for their use of the use of the term "and" with plural nouns, on the grounds that this usage renders the claims vague. Accordingly, Claims 1, 2, and 4 (last lines thereof) have been amended to recite singular forms of the claimed nouns.

In view of the foregoing amendments to the claims, applicants believe that the Examiner's objections under 37 C.F.R. § 112, second paragraph have been addressed. Withdrawal of the rejections is therefore respectfully requested.

**Rejections under 35 U.S.C. § 112, first paragraph**

Claims 7 and 8 stand rejected under 35 U.S.C. § 112, first paragraph on the grounds that the specification, while being enabling for treating asthma, allegedly does not reasonably provide enablement for treating all diseases or any diseases generically embraced in these claims. It is the Examiner's position that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use of the invention commensurate in scope with these claims.

Claim 8 has been canceled by virtue of this amendment. Claim 7 is directed to a method of treating an inflammatory condition in a mammalian patient which condition is mediated by VLA-4. Newly presented claims 9 and 10 have been added to bring out the feature of the invention that the inflammatory conditions that are particularly amenable to treatment, using compounds of the present invention, are inflammatory arthritis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses, asthma and inflammatory bowel disease.

The test of enablement is whether the applicants have taught how to make and use the invention as claimed.

As a matter of Patent Office practice... a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of §112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971).

Further the court in *Marzocchi* has stated, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." MPEP 2164.04; *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971).

Applicants have described in detail in the specification how to make compounds in accordance with the invention, how to formulate such compounds into a variety of forms suitable for administration to mammalian subjects, and appropriate dosage schedules for such administration (see, for example, paragraphs [00143]- [152] found at pages 51-53 of the instant specification).

Further, the applicants have described in detail how binding of the integrin alpha chain,  $\alpha 4$ , to either of beta chains  $\beta 1$  (to form the integrin VLA-4) or  $\beta 7$  (to form the integrin LPAM-1), and, in turn, these  $\alpha 4$  integrin molecules interact with VCAM-1/fibronectin and MAdCAM-1, respectively. The applicants have also described how such  $\alpha 4$  integrin binding events, particularly those associated with inhibiting VLA-4 have been shown to be involved in a number immune or inflammatory disease states (see, for example paragraphs [0007] to [0010] found at pages 2-4, and paragraphs [00141] – [00142] at page 51 of the instant specification). According to an important discovery of the present invention, compounds of the invention are potent and selective inhibitors of these specific  $\alpha 4$ - $\beta 1/\beta 7$  interactions (see, for example, paragraph [0010] at page 4 of the instant specification). Applicants have further provided guidance for selecting potent and selective alpha-4 integrin inhibitory agents using established *in vitro* and *in vivo* assays (see, for example, paragraphs [00380] to [00387] found at pages 129-131 of the instant specification, and have provided guidance for the specific inflammatory indications (inflammatory arthritis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses, asthma and inflammatory bowel disease; paragraph [00142]) for which evidence exists that agents having the integrin binding inhibitory activities of the compounds of the invention would be useful.

Accordingly, applicants submit that they have provided sufficient guidance to enable persons skilled in the art to make and use the invention as presently claimed. The Examiner has not provided any documentation or evidence as to why it doubts the truth or accuracy of applicants' assertions in this regard.

In view of the foregoing amendments and remarks, applicants respectfully submit that the instant specification complies with the enablement requirements of 35 U.S.C. § 112, first paragraph. Accordingly, withdrawal of the objections and rejections thereunder are respectfully requested.

**CONCLUSION**

Applicants respectfully submit that all issues raised in the Office action have been properly addressed in this response and that the claims pending in the application are now in condition for allowance. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, she is encouraged to contact the undersigned at the telephone number provided below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-2859** referencing docket no. 428372000500. However, the Assistant Commissioner is not authorized to charge the cost of the Issue Fee to the Deposit Account.

Dated: December 16, 2003

Respectfully submitted,

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